THIN-FILM PERIPHERAL NERVE ELECTRODE

FINAL REPORT

SBIR PHASE I RESEARCH

Contract No. N43-NS-2-2367

for Period September 28, 1992 to March 26, 1993

by

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June 2, 1993

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1.0 INTRODUCTION AND SUMMARY

1.1 Summary of Major Results

The Phase I program sought to demonstrate the feasibility of fabricating thin film neural cuff electrodes on thermoformable polymer substrates using vacuum deposited metallization for the electrical leads and charge injection sites. Photolithographically patterned bilayer films of Ti and Ir could be sputtered onto FEP Teflon® film (0.002 inches thick) and remain adherent following 240 hr soak tests in 0.1M PBS at 90°C and steam sterilization at 13 psig and 120°C for 20 minutes. Low sheet resistivity, ~0.25 Ω/sq., Ti-Ir-Ti-Au coatings for electrical leads were also adherent following soaking and sterilization. Substrate biasing during deposition of the Ti layer adjacent to the FEP Teflon® was the most important variable influencing adhesion of the metallization. Thin films of a fluoropolymer (DuPont, Teflon® AF) applied by spinning and solvent evaporation provided the most effective insulation for the metallization on the interior surface of the cuff. The TiIr bilayers could be activated to form anodic iridium oxide (AIROF) charge injection electrodes. The AIROF films on FEP Teflon® were evaluated in acute tests using anodal and cathodal pulses at 80 $\mu C/cm^2$. There was no evidence of electrochemical degradation of the AIROF following these acute studies, but morphological changes were observed by scanning electron microscopy. Nerve cuff electrodes were fabricated by thermoforming metallized Teflon® films and evaluated *in vivo* for passive (no stimulation) nerve tolerance in a 42 day study using the cat sciatic nerve. No significant nerve degradation was observed and observations support the recent contention that snug fitting cuffs capable of accommodating post-operative edema without undue pressure on the nerve are physiologically well tolerated.

1.2 Program Objective

A program to develop an FNS system capable of graded and stable activation of hand muscles for the restoration of grasp in quadriplegic individuals has been proposed. The overall objective of the program is the development of a thin film neural cuff electrode and the demonstration of the efficacy of the electrode for grasp in an *in vivo* study using a raccoon model.

Specific features of the proposed electrode include:

- multiple, independently addressable charge injection sites that will facilitate implementation of established and emerging stimulation protocols such as anodal field steering and anodal blocking;
- leads and electrodes are vacuum deposited on a planar, monolithic fluorocarbon substrate that is flexible and avoids bulky interconnects in close proximity to the implantation site;
- charge injection electrodes of Pt or anodized iridium oxide (AIROF), both of which are stable under the anticipated charge injection protocols;
- fluorocarbon substrates (FEP Teflon®) that can be thermoformed into a self-sizing cuff to allow a snug but elastic fit to the nerve.

1.3 Thin Film Peripheral Nerve Electrodes

The circumneural electrodes are fabricated by vacuum depositing metal films on thin sheets of fluorocarbon polymer and photolithographically patterning and the leads and charge injection sites. The patterned substrate is then thermally sealed with a second polymer layer to electronically isolate the leads from the physiological environment. The charge injection sites are exposed by a combination of photolithography and ion or plasma etching of vias through the polymer overlayer. Once all planar fabrication processes, i.e., photolithography, vacuum deposition, and etching have been completed, the electrode is cut out of the substrate and the desired cuff and lead geometries created by thermoforming.

An example of an electrode in planar geometry prior to thermoforming the cuff is shown in Figure 1A. The leads and charge injection sites are patterned on a large polymer substrate with the leads extending to a bonding pad that is located a significant distance proximal to the cuff. Four charge injection sites, in a "round about" geometry, similar to that being investigated for phrenic nerve stimulation (Baer *et al.*, 1990), are shown on the cuff. Optional perforations through the cuff and a suturing tab are also indicated. Examples of other geometries for circumneural or hemineural charge injection are shown in Figures 1B and 1C.

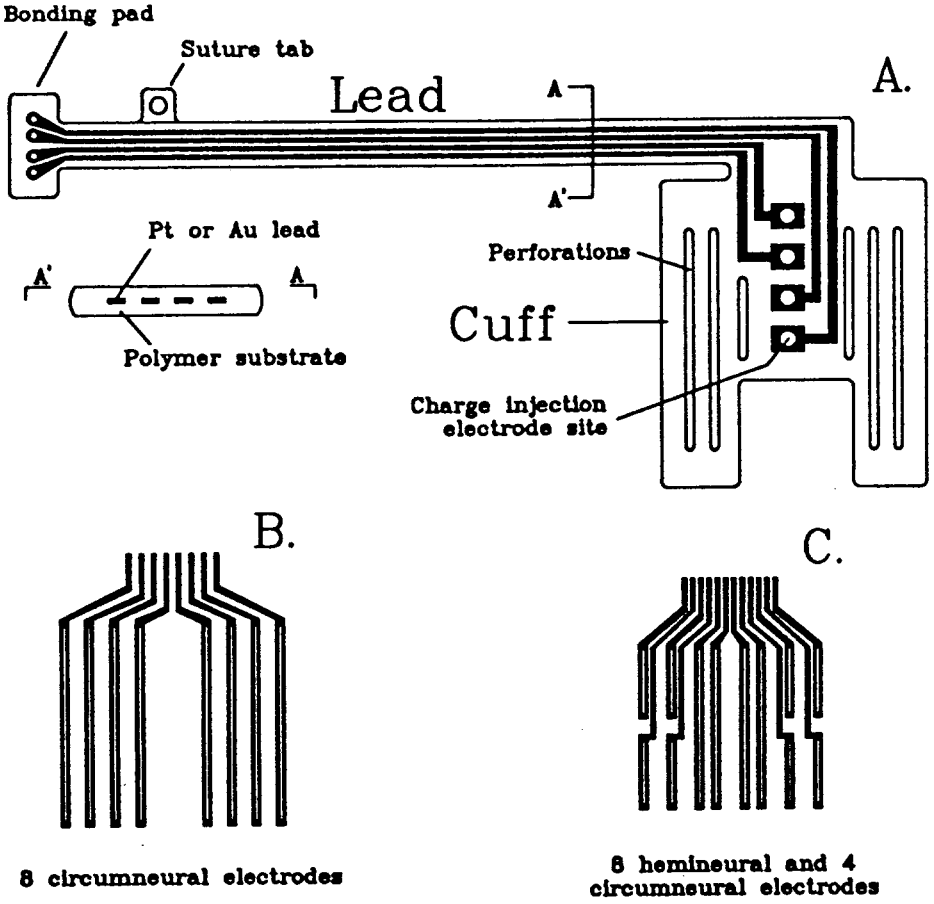

Figure 1. A) a circumneural cuff having four "round about" charge injection sites, perforations, interconnect bonding pad, and suture tab; B) an electrode pattern with 8 circumneural charge injection sites; C) an electrode pattern with circumneural and hemineural charge injection sites.

Geometry and Size. Grasp is controlled primarily by the median nerve. In the human forearm, this nerve is obloid with a diameter of about 4 mm. The branches of the nerve in the hand itself are smaller, ~2 mm. Since the median nerve in the proposed raccoon model is also about 2 mm in diameter, this size was chosen for the Phase I electrode development. The cuff diameter allows sufficient overlap in the transverse direction that complete circumneural coverage is retained while allowing a minimum 25% increase in cuff diameter. The increase in diameter prevents constriction of the nerve due to post-operative edema, limits tissue growth between the cuff and the nerve, and also avoids extrusion of tissue through the longitudinal opening, a characteristic problem with some split-cylinder cuffs (Naples *et al.*, 1990). From a practical standpoint, the cuff will be limited to about 1.5 cm in length for the animal studies. If necessary, portions of the cuff not housing the electrodes will be perforated to allow contact between the nerve and the tissue fluids (see Figure 1A). The cuffs are implanted around the nerve using modified tweezers, in a manner similar to that described by Bullara (1990).

Stimulation protocols for cuff electrodes typically involve currents of less than 3 mA and pulse durations on the order of 150 μS. A 1 mm^2 area electrode would, therefore, be required to inject a maximum of 45 $\mu C/cm^2$. This charge density is within the acceptable range for Pt or AIROF for both anodal and cathodal pulses. If smaller electrodes or higher charge densities are required, the AIROF would be preferred because of its higher charge injection capacity (Robblee and Rose, 1990).

Lead and Electrode Metallization. The electrical leads run continuously from the charge injection site to the bonding pad so that interconnects or other mechanical fixtures in close proximity to the cuff are avoided. Since a large number of very thin conductors can be patterned along a narrow lead, maximum flexibility between the cuff and bonding pad is obtained. The noble metals Au, Pt, and Ir were chosen as lead materials because of their high electrical conductivity and established biocompatibility. Table 1 lists some relevant properties of the lead materials. Because the lead in the present design is about 10 cm long, a major consideration in sizing the conductors is minimizing electrical resistance. Based on bulk electrical resistivity values, the resistance of a 200 x 0.5 μm lead 10 cm long is ≤100Ω for all three metals. Pt has a useful combination of ductility, conductivity, and charge injection capacity. Although the Au lead has the lowest resistance, it cannot be used for charge injection (Robblee *et al.*, 1991). In Phase I we investigated two lead configurations: 1) a Ti/Pt bilayer lead and electrode site; 2) a Ti/Ir/Au trilayer and Ti/Ir/Ti/Au four-layer lead with AIROF at the electrode site.

Table 1. Properties of Lead and Electrode Materials for Thin Film Cuff Electrode

Property	Gold	Platinum	Iridium
Electrical Resistivity at 20°C (microohm-cm)	2.13	9.85	5.11
Resistance of 10 cm Lead, 200 μm Wide and 0.5 μm Thick	20	100	50
Linear Coefficient of Expansion (/°C)	14.2×10^{-6}	9.1×10^{-6}	6.8×10^{-6}
Young's Modulus of Elasticity (psi)	11.2×10^{6}	24.8×10^{6}	76×10^{6}
Tensile Strength (psi)	18,000	20,000	160,000
Reversible Charge Injection Limit ($\mu C/cm^2$)	<20	50-150	1000-4000 (activated)

Multiple Charge Injection Electrodes. Recent studies suggest that selectivity and gradation are possible with cuff or helical nerve electrodes when sufficient latitude in the number and geometry of charge injection sites is provided (Baer *et al.*, 1990; Fang and Mortimer, 1991a,b). Electrode designs or stimulation protocols that might be employed with cuff electrodes include: monopolar from a single or multiple sites with the implanted stimulator as the indifferent electrode; six position "round about" stimulation at two locations; bipolar between longitudinal and transverse electrode pairs; anodal blocking; collision blocking; and combinations of these. The anodal field steering technique recently demonstrated on the cat sciatic nerve by Sweeney *et al.* (1990) may be particularly appropriate for grasp using the median nerve because of the generally similarity in fascicular localization between these nerves.

Substrate Material. Critical requirements for the polymer substrate are biocompatibility, flexibility, low moisture and ion permeability, and suitability for thermal forming and sealing operations. The properties of four commonly used fluorocarbon polymers which meet these requirements are listed in Table 2. Initially we selected FEP, PFA, and ETFE (Tefzel) for the Phase I study. The polymers are thermoplastic and are easily heat sealed and thermoformed. ETFE is somewhat stiffer and more robust than FEP, but FEP has better heat sealing characteristics. All three materials are available as thin sheets (0.012 to 2 mm thick) from DuPont and can be obtained with the surface treated by corona discharge to improve adhesion.

Mechanically induced neuropathy, particularly by force transmission through the lead, is a significant concern with nerve electrodes (Naples *et al.*, 1990). The flexibility inherent in the thin polymer films will minimize mechanical interaction between the lead and cuff, reducing mechanical strain on the nerve. The flexibility of the lead and cuff portions of the electrode will be controlled by the thickness of the polymer substrate. A thin polymer layer, <25 μm thick to minimize stiffness and provide close access of the electrodes to the nerve, has been proposed to electrically isolate the metal leads from the physiological environment. The lead portion of the electrode can also be formed into various spiral and waffled structures to decrease longitudinal and transverse stiffness and increase flexibility, if required.

An abbreviated list of the technical objectives of the Phase I program is provided below.

1.4 Phase I Technical Objectives

The Phase I program sought to demonstrate the feasibility of thin-film peripheral nerve electrodes and to evaluate *in vivo* the extent of mechanical damage caused by the implanted cuff. The specific technical objectives were the following:

1. To demonstrate sputter deposition of films of Au and Pt for the lead and electrode on heat sealable thin fluorocarbon polymer (FEP and ETFE) substrates, and to develop strong metal-polymer adhesion by the following:
   - preparation of the polymer surface by reactive plasma treatment;
   - use of Ti and Ta reactive metal interlayers;
   - optimization of sputter deposition conditions;
   - use of RF substrate biasing.
2. To develop methods of patterning the leads and electrodes by photolithography. The following thin-film structures were anticipated:
   - FEP/Pt and FEP/Au with and without the Ti or Ta interlayer;
   - ETFE/Pt and ETFE/Au with and without the Ti or Ta interlayer.

3. To fabricate planar electrode structures with single and multiple electrode sites. Anticipated fabrication procedures included:
   - thermal lamination with a thin film of FEP or ETFE overlayer;
   - plasma etching of electrode vias through the overlayer.
4. To thermoform planar electrodes into circumneural cuffs with flexible spiral leads.
5. To conduct *in vitro* evaluation of the electrodes at the different stages during their fabrication. Anticipated evaluation procedures included:
   - accelerated testing in 0.1N PBS at 90°C to evaluate integrity of the laminated structure and lead/electrode adhesion;
   - electrochemical characterization by cyclic voltammetry and charge injection studies in 0.1N PBS;
   - measurement of tensile mechanical properties;
   - optical and scanning electron microscopy evaluation before and after testing.
6. To perform *in vivo* studies of implanted circumneural electrodes in the cat. The anticipated methodology involved:
   - implanting electrodes on the median nerve for a minimum period of six weeks;
   - documenting the degree of edema, fibrous tissue encapsulation, and general pathology of the nerves at time of autopsy;
   - performing a histological study of the subject nerves.

Table 2. Properties of fluorocarbon polymers considered in the Phase I program.

Property	TFE	FEP	PFA	ETFE
Registered Trademark Names	Teflon®	Teflon®, Neoflon	Teflon®, Neoflon	Tefzel, Halon ET, Neoflon
Composition	tetrafluoro-ethylene	tetrafluoro-ethylene/hexa fluoropropylene	tetrafluoro-ethylene with ether linkages	tetrafluoro-ethylene/ ethylene
Melting Point (°F)	620	487-540	575-590	520
Ultimate Elongation, %	225-450	300	300	100-300
Ultimate Tensile Strength (psi)	2,500-4,000	3,000-4,000	4,000	6,500-7,500
Heat Sealable	no	yes	yes	yes
Themoplastic	no	yes	yes	yes

2.0 PHASE I RESULTS

2.1 Sputter Deposition of Lead and Electrode Metallization

The initial task of the Phase I program was to develop sputter deposition conditions for coating fluoropolymer substrates with the lead and electrode metallization. The three substrate materials investigated were FEP (fluorinated ethylene propylene copolymer) Teflon®, PFA (perfluoroalkoxy polymer), and TEFZEL® (ethylene-tetrafluoroethylene copolymer). All three polymers are fully or partially fluorinated, have a high degree of chemical stability, and can be thermally molded or shaped (thermoformed) without melting. The FEP and TEFZEL® were available from the manufacturer with a corona discharge treated surface to improve wettability and adhesion.

Prior to coating, the substrates were cleaned by soaking in a 2:1 mixture of concentrated H_2SO_4 and 30% H_2O_2 followed by thorough rinsing with deionized H_2O and an oxygen plasma treatment for 15 minutes. The substrates were mounted on optically transparent, electrically conductive plates (Corning 7059 glass with a 15 Ω/sq. tin-doped indium oxide coating) that were electrically isolated from the substrate holder and vacuum chamber. The conductive plates were electrically connected to an external RF power supply, allowing the substrates to be plasma cleaned *in vacuo* or electrically biased during sputter deposition. Based on initial experimentation, a predeposition protocol was developed and used for all subsequent depositions. The protocol was as follows: evacuate the deposition chamber to a base pressure of 9×10^{-6} torr; radiantly heat the substrates at 90°C for 10 minutes; backfill the chamber with oxygen to a pressure 10 millitorr and plasma clean the substrates for 2 minutes by applying 0.4 watts/cm^2 of RF power (13.56 MHz frequency) to the conductive plate.

Adhesion of the metallization was evaluated in a qualitative manner. As-deposited films were screened for adhesion using a standard tape peel test. Those films that adhered were then soaked in 0.1M phosphate buffered saline (PBS) (pH 7.2) at 90°C for a minimum of 16 hr and adhesion reevaluated with the tape test. Those films that remained adherent following the soak test were considered to have "passed" and were used in subsequent evaluation and cuff fabrication procedures.

2.1.1 Titanium Deposition

Titanium is frequently used as an adhesion layer for noble metal coatings because of its tendency to chemically reduce and hence adhere to a wide variety of substrate materials. Although titanium is not expected to reduce fluorinated hydrocarbons to a significant degree, we anticipated using plasma modified surfaces as a means of promoting film adhesion. Since the plasma modification results in derivatization of the polymer surface with more reactive species (hydroxyl groups, for example), titanium was adopted as an adhesion layer prior to all noble metal (e.g., Au, Pt, and Ir) deposition.

Titanium Sputtering.

The initial investigation of Ti deposition involved DC sputtering onto electrically floating substrates. Typical deposition conditions were as follows: Ar sputter gas at a pressure of 10 millitorr; 150 mA constant current discharge at a cathode voltage of 290-300 V; 5.5 cm target-to-substrate distance; and a 2 minute sputter time. The substrate temperature was not controlled. These deposition conditions were chosen because previous experience has shown

them to produce adherent Ti films on glass and silicon substrates. Regardless of the type or treatment of the polymer substrates, none of the Ti films deposited under these conditions was adherent following soaking in PBS at 90°C.

Substrate Biasing.

The use of substrate biasing as a means of controlling the morphology, density, and adhesion of sputtered films is well known (Windischmann, 1991; Thornton, 1977). Changes in film properties are brought about by an increase in the flux and energy of species bombarding the substrate during deposition. In the case of metal deposition on polymers, substrate biasing can improve adhesion by physical mixing at the metal polymer interface due to implantation of the metal atoms below the polymer surface.

Polymer substrates were RF biased at a range of power levels that produced a net DC bias ranging from -30 V to -100 V. A net DC bias occurs because of the difference in mobility of electrons and cations in the plasma and is measured with a DC voltmeter protected by an RF filter with a >80 dB drop at 13.56 MHz. In Table 3, the adhesion of Ti films deposited at various levels of substrate biasing on different polymers is listed. The Ti deposited on 0.002 inch (50 μm) thick FEP at a -75 V bias and on 0.002 inch (50 μm) thick PFA at a -30 V bias were both adherent following 90°C soaking in PBS. The as-deposited Ti surfaces were visually smooth and reflective. There was no apparent beneficial effect of the corona discharge treatment on adhesion and all subsequent depositions were performed on untreated surfaces.

The effect of substrate bias on the adhesion of Ti to FEP Teflon® can be clearly seen from the data presented in Table 4 which compares the adhesion of Ti films at different bias voltages for short and longer time exposure to PBS at 90°C. Although the data is qualitative, the relationship between higher bias voltages and improved adhesion is readily apparent. Due to morphological changes on the surface of the polymer substrate at the -100 V bias, -75 V was adopted as a standard bias for Ti deposition.

Following the success of the biasing with FEP and PFA substrates, it was decided at this point in the program to focus exclusively on 0.002 inch thick FEP as the primary cuff material. The FEP was chosen because of the Ti adhesion results, availability in thinner sheets than the PFA, and its established biocompatibility and acceptance as a chronic implant material.

Plasma Modification.

The addition of reactive functional groups to the surface of a polymer is an established technique for improving adhesion of metal films. Plasma modification to derivatize a variety of polymers with carbonyl (-C=O) and hydroxyl (-OH) functionality has been reported (Lindsay and LaSala, 1985; Cho and Yasuda, 1986; and, Vargo *et al.*, 1991 and 1992). Chemical derivatization to introduce hydroxyl, amino, and carboxylic functionality can also be accomplished with fluorocarbon polymers but was not investigated in this program (Costello and McCarthy, 1987).

Table 3. Tape test adhesion results for Ti films deposited with a RF substrate bias.

Polymer	Substrate bias V DC	Tape Test As-deposited	Tape Test Soak in PBS @ 90°C
Tefzel	-22 (floating)	fail	fail
(0.005 inch thick)	-50	pass	fail
	-100	fail	fail
FEP	-22 (floating)	pass	fail
(0.005 inch thick)	-50	fail	fail
	-100	fail	fail
FEP	-23 (floating)	fail	fail
(0.002 inch thick)	-75	pass	pass
PFA	-22 (floating)	pass	fail
(0.002 inch thick)	-30	pass	pass
	-85	pass	fail

Table 4. Tape test adhesion results for Ti films sputter deposited on FEP Teflon® as a function of substrate bias.

Applied Bias Volts	Results of Tape Test As-deposited	90°C PBS, 15 min	90°C PBS, 60 hr
-100	pass	pass	pass
-75	pass	pass	pass
-50	pass	pass	washed off
floating	pass	fail	washed off

Hydroxylation of FEP substrates as a means of further improving Ti adhesion was investigated using the hydrogen/methanol plasma treatment described by Vargo *et al.* (1991). In our system, methanol was introduced into the vacuum chamber by pumping on an external methanol reservoir through a needle valve. Hydrogen gas was introduced through a mass flow controller. The methanol and hydrogen gas partial pressures were monitored with a residual gas analyzer and set to 26 millitorr and 74 millitorr, respectively. A plasma was generated by applying 3-4 watts of RF power to the substrate which resulted in a net DC bias of -70 volts. The plasma treatment time was 15 minutes. Samples of derivatized FEP removed from the chamber were easily wetted with water suggesting a significant degree of functionalization. There was no evidence of physical damage to the treated FEP.

Titanium films deposited on the treated FEP without substrate biasing showed a marginal improvement in adhesion in the as-deposited condition while no treated and unbiased Ti films adhered following 90°C soaking in PBS. Films deposited on plasma modified FEP with substrate biasing (-75 V) passed the adhesion tests although the test protocol was unable to distinguish between plasma treated and untreated substrates when RF biasing was used. Since no benefit from plasma modification was apparent for films deposited with RF biasing, this process was not employed as a surface treatment for subsequent multilayer metallization.

2.1.2 Titanium/Iridium Deposition

Iridium was evaluated as metallization on the cuff electrodes because of the option of activating the charge injection sites to produce anodic iridium oxide films (AIROFs). The utility of AIROF as a high charge capacity electrode material capable of bipolar operation has been described in detail (Robblee *et al.* 1983; Robblee and Rose, 1990).

Titanium films, sputtered with a -75 V substrate bias, were used as an interlayer between the FEP substrate and Ir films. Initially, the Ir was sputtered without substrate bias at a pressure of 22 millitorr of Ar. The as-deposited Ti-Ir bilayers were specular in appearance but the FEP substrate developed coarse undulations associated with relaxation of stresses in the as-deposited films or thermal distortion due to excessive substrate heating during the Ir deposition. The as-deposited Ti-Ir metallization was, however, adherent when evaluated by tape testing.

To minimize substrate heating, the DC current during Ir deposition was decreased from 150 mA to 100 mA and the target-to-substrate distance increased from 4.5 cm to 6.5 cm. Additionally, the 22 millitorr sputtering pressure was decreased to 10 millitorr because of our observations on glass substrates that compressive-to-tensile stress transitions occur around 18-22 millitorr and we wished to avoid the situation in which the film properties might be sensitive to small variations in the deposition conditions. With the new deposition conditions, no substrate distortion was observed and the as-deposited Ti-Ir bilayers were quite adherent. A variation in the film morphology, however, was apparent depending on whether the coated region of the substrate was located directly under the magnetron or displaced to one side. The films had a hazy appearance under the magnetron but were otherwise specular. This difference in morphology is presumably due to bombardment of the substrate from the higher flux of energetic species that originate from the central region of the target during magnetron sputtering. Substrate biasing did not have a noticeable effect on the adhesion of the Ir films to the Ti, although a -75 V bias during Ti deposition was always necessary to ensure adhesion of the bilayer.

The Ti-Ir films, with either the specular or hazy morphology, passed adhesion testing following extended soaking in PBS at 90°C. The electrical conductivity of the as-deposited films was evaluated using a four-point-probe measurement of sheet resistivity. The regions with the hazy morphology typically had a sheet resistivity of ~6 Ω/sq. while the specular regions had a resistivity of ~4 Ω/sq.

As a final evaluation of adhesion, Ti-Ir bilayers were steam sterilized in an autoclave at 120°C and 13 psig for 20 minutes. The sterilization process produced no deformation of the substrates and the metallization remained adherent during post-sterilization tape testing.

2.1.3 Titanium/Platinum Deposition

Deposition of adherent Pt on Ti-coated FEP Teflon® proved more difficult than deposition of Ir films. In the as-deposited condition, most Ti-Pt bilayers passed the tape test but all failed extended soak tests in PBS at 90°C. Failure was generally observed as delamination of the Ti at the Ti-FEP interface. Substrate biasing during Pt deposition had no effect on adhesion, even at bias voltages of -100 V. Predeposition derivatization of the FEP with -OH groups also provided no improvement in adhesion following soaking in PBS at 90°C.

The as-deposited Ti-Pt films were specular in appearance and showed the least disruption of the FEP surface. The effects of energetic bombardment due to position relative to the center of the magnetron were also least evident with the Ti-Pt films.

2.1.4 Titanium/Iridium/Gold Deposition

The electrical resistance of the thin film leads connected to the charge injection sites on the cuff should be as low as possible to minimize the energy required to deliver a stimulation pulse. Low lead resistance and power consumption will be particularly important for thin film cuffs used in totally implanted systems where battery capacity or RF power transmission may limit lifetime or performance. The Ti-Ir bilayers have a sheet resistance of ~5 Ω/sq. which could introduce significant resistance in photolithographically patterned thin film traces. To minimize lead resistance, a thin Au film was deposited over the Ti-Ir bilayer using the same deposition conditions for the Au as employed for Ir.

The Au films did not adhere well directly to Ir unless they were sputtered with a -75 V substrate bias or unless a thin Ti layer was used as an adhesion promoter. The Ti adhesion layer between the Ir and Au was sputtered at a floating substrate potential. The multilayer structures deposited with the Ti adhesion layers or biasing during Au deposition passed the adhesion tests following an extended soak of 240 hr in 90°C PBS. The as-deposited Ti-Ir-Ti-Au four-layer coatings had a sheet resistivity of ~0.25 Ω/sq.

2.1.5 Planetary Sputtering

To minimize morphological damage during sputter deposition of the metallization, the planetary system on which the polymer substrates are mounted was connected to an external, computer controlled stepper motor so that the substrates could be moved continuously through the plasma during deposition. By oscillating through an arc of about 120°, the substrate could be moved from directly under the magnetron to entirely out of the deposition zone. Using an oscillation frequency of 0.25 Hz and increasing the deposition times by a factor of 4, produced significantly more uniform and specular films. Substrate biasing and *in situ* cleaning were still used during the deposition. Using this technique, a greater fraction of the film deposition occurs outside the region of highest energetic bombardment and less disruption of the substrate is anticipated. No compromise in adhesion was observed using the oscillating substrate holder.

Scanning electron microscopy of metallized FEP Teflon® revealed a fine network of defects that appear to be "folds" in the metallization. An example of this structure is shown in Figure 2 for a Ti-Ir coating. The folded structure is consistent with the relaxation of compressive stresses in the metallization. Since substrate biasing tends to increase compressive stresses, the Ti adhesion layer was sputtered for the first half of the deposition at a -75 V bias and allowed to float for the

remainder of the deposition time. This procedure produced adherent Ti films that passed the tape test after steam sterilization and were also free from "folds" or other defects associated with the relaxation of compressive stress.

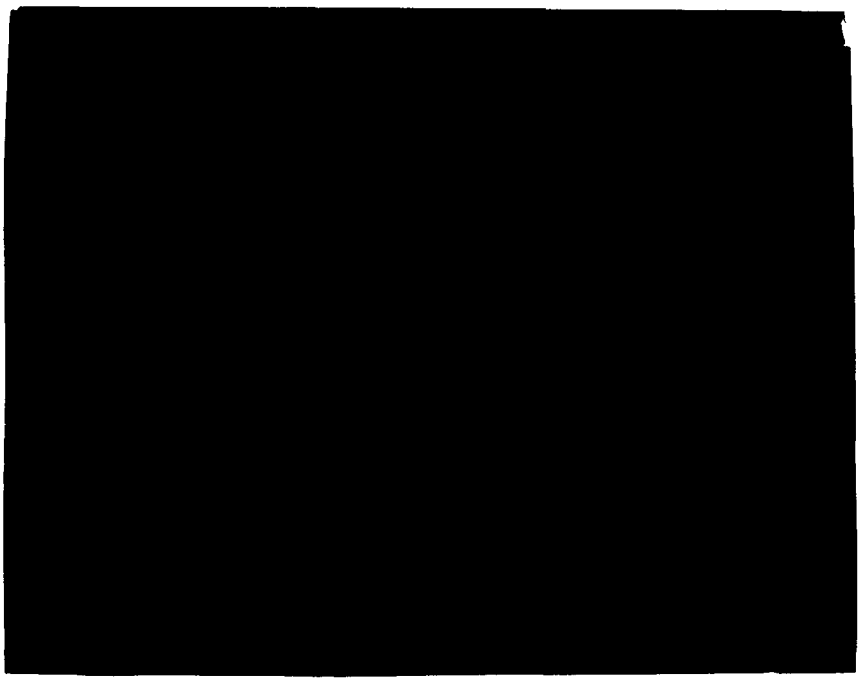

Figure 2. Scanning electron micrograph of Ti-Ir metallization sputtered onto FEP Teflon® with a -75 V substrate bias.

2.2 Photolithographic Patterning

Photolithography is required to define the metallization for the charge injection sites and the conductive traces leading to these sites. Both the subtractive process in which metallization is deposited over the entire substrate and selectively removed by etching and the liftoff process in which metallization is deposited over patterned photoresist and subsequently removed by stripping the resist were investigated. The liftoff process was eventually chosen for cuff fabrication because the metallization under the resist exhibited poor adhesion when etching with the very aggressive media required to remove Ti and Ir.

In order to obtain adherent and uniform photoresist coverage, it was necessary to clean the FEP Teflon® with a 2:1 mixture of concentrated H_2SO_4 and H_2O_2 (30%) and to oxygen plasma clean for 15 minutes. A Shipley 1800 positive photoresist was spun on the Teflon® at 3500 rpm for 25 seconds and soft baked at 100°C for 30 minutes. The photoresist was exposed through a Cr mask using an Oriel UV exposure and mask alignment system. Following UV exposure the resist was developed in a Shipley CD-30 developer and rinsed in deionized H_2O.

Metallization was sputtered over the patterned photoresist using the *in vacuo* cleaning and deposition conditions described previously. After deposition, the unwanted metallization was stripped from the substrate by soaking in acetone and gently abrading the surface with a cotton swab. Following liftoff, the patterned substrates were rinsed in distilled H_2O and inspected under an optical microscope. A scanning electron micrograph of Ti-Ir-Ti-Au metallization is shown in Figure 3.

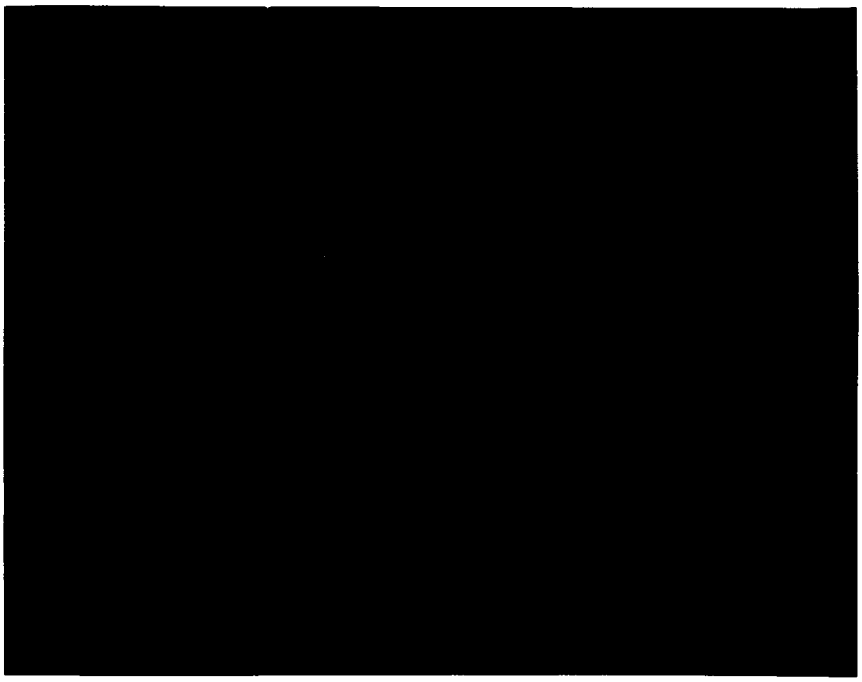

Figure 3. Scanning electron micrograph of Ti-Ir-Ti-Au metallization after patterning to form conductive leads. The width of an individual lead is 0.25 mm (0.01 inches).

2.3 Fabrication of Cuff Electrodes

2.3.1 Multisite Electrode Preparation

The photolithographic procedure described above was used to pattern substrates for both *in vitro* and *in vivo* evaluation. The geometry and dimensions of the substrates and metallization evaluated are shown in Figures 4 and 5. The metallization on the cuff electrode in Figure 4 comprises of Ti-Ir for the charge injection sites and Ti-Ir-Ti-Au for the leads. The pattern shown in Figure 5 was used to evaluate the etch and liftoff processes.

2.3.2 Inner Surface Passivation and Insulation

A patterned insulating layer is required on the internal surface of the cuff to define the charge injection sites and isolate the electrical leads from the physiological electrolyte. Several approaches were investigated in the Phase I program. The primary requirements of the insulation are good barrier properties to prevent ion and H_2O transport, low electronic conductivity, flexibility, and adhesion to metals and Teflon®.

FEP Teflon® and Polypropylene Laminates.

Thin, standalone films of FEP Teflon® and polypropylene were investigated as inner surface insulation. The films were laid over the metallized FEP Teflon® substrates and laminated under heat and pressure. No lamination conditions for FEP Teflon® were found which produced adequate adhesion to both the FEP Teflon® and metallization. Lamination at high temperatures, 275°C, caused unacceptable flow of the Teflon®. In an effort to reduce the lamination temperature, thin films of polypropylene were investigated as inner surface insulation. Even at elevated temperatures (250°C) and pressures of 5000 lb/in^2, the polypropylene could not be made adherent to the Teflon® substrate.

Dielectric Deposition.

As an alternative to lamination, plasma enhanced chemical vapor deposition (PECVD) was investigated as a means of depositing thin film dielectrics such as Si oxide, Si oxynitride, and Si nitride over the metallization. Typically, PECVD involves substrate temperatures on the order of 300-350°C which would cause degradation of the FEP substrates. Deposition conditions with lower substrate temperatures (~120°C) but compensatory higher RF power levels were developed. Deposition of the dielectrics caused significant curling of the substrate in keeping with the development of compressive stresses in the dielectric. The direction of the curl is opposite to that required in forming the cuff. The curl could be removed by turning the substrate over and depositing dielectric on the reverse side. With this procedure, flat FEP films with approximately 300 nm films of dielectric on both surfaces could be produced.

Although the as-deposited dielectrics were adherent to the FEP polymer, they rapidly delaminated on soaking in PBS at 37°C. The adhesion was poor regardless of the specific dielectric. Improving adhesion of the dielectrics directly to the metallization should be possible, particularly if the substrate temperature is increased and a thin Ti adhesion layer deposited over the Au. Further investigation in this area, however, was beyond the scope of the program.

Spun Teflon® Films.

Thin films of Teflon® can be deposited by spin coating from solutions of polymer dissolved in a perfluoroalkyl solvent. This material is commercially available from DuPont under the tradename Teflon® AF. The precise composition of the polymer appears to be proprietary but it is a copolymer of perfluoro(2,2-dimethyl-1,3-dioxole) and tetrafluoroethylene with physical and chemical properties similar to PTFE or PFA Teflon®. The solvent is a product of the 3M Company sold under the tradename Fluorinert FC-75. The polymer is dissolved rather than emulsified by the solvent and extremely thin films can be formed on a variety of substrates by either spinning or dipping.

The Teflon® AF was obtained from DuPont as an 18% by weight solution of the polymer in the solvent. At this concentration of polymer, the solution is too viscous to be spun as a thin film and was further diluted by the addition of Fluorinert FC-75. A satisfactory spin procedure involved adding Fluorinert to Teflon® AF in a 2:1 weight ratio and spinning at 1500 rpm for 60 seconds. Following spin coating, the solvent is removed from the Teflon® AF film by a sequence of thermal processing steps designed to evaporate solvent and densify the coating without causing mechanical disruption. Once fabricated, the films were examined by scanning electron microscopy and the quality of the insulation evaluated by DC leakage current measurements of coated metallization immersed in phosphate buffered saline (PBS) at 37°C and pH 7.4.

The experimental apparatus for DC leakage current measurements is shown schematically in Figure 6. The coated substrates were hung in a beaker of 0.1 N PBS that also contained a large area Pt counter electrode. The entire apparatus is mounted in a Faraday cage inside a biological incubator maintained at 37°C. The Faraday cage was isolated from the incubator and electrically tied to the low side of the voltage output on the electrometer. The leakage current was measured as a function of voltage bias between ±5 V. The typical experimental protocol involved stepping the voltage from zero to 5 V, down to -5 V, and back to zero in 1 volt increments. It requires about 12 hrs of data acquisition time to generate a single cycle IV curve. A more detailed description of the test procedure and statistical analysis methods have been reported by Edell *et al.* (1989).

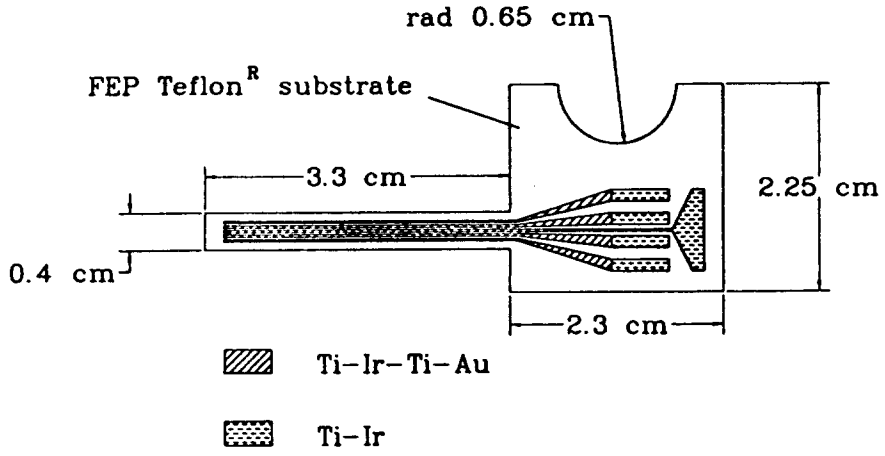

Figure 4. Electrode and lead metallization on a cuff electrode prior to thermoforming. The electrodes are the Ti-Ir areas. The Ti-Ir-Ti-Au leads are coated with a polymer for electrical isolation.

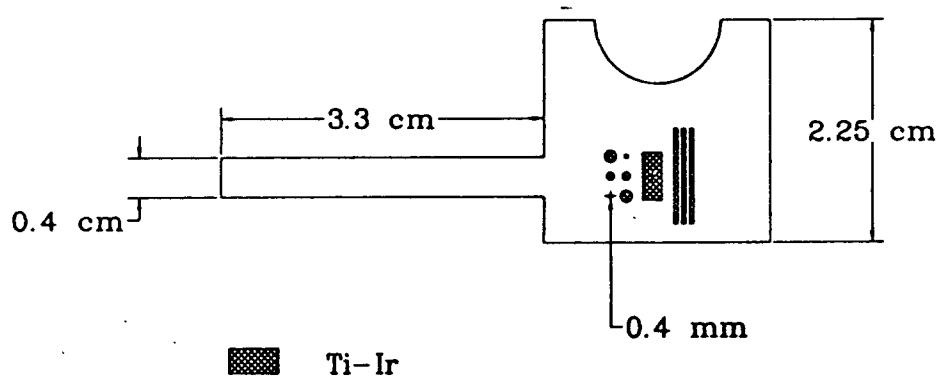

Figure 5. A second metallization geometry used to evaluate the photolithographic liftoff process. The minimum feature size is an 0.4 mm diameter circle.

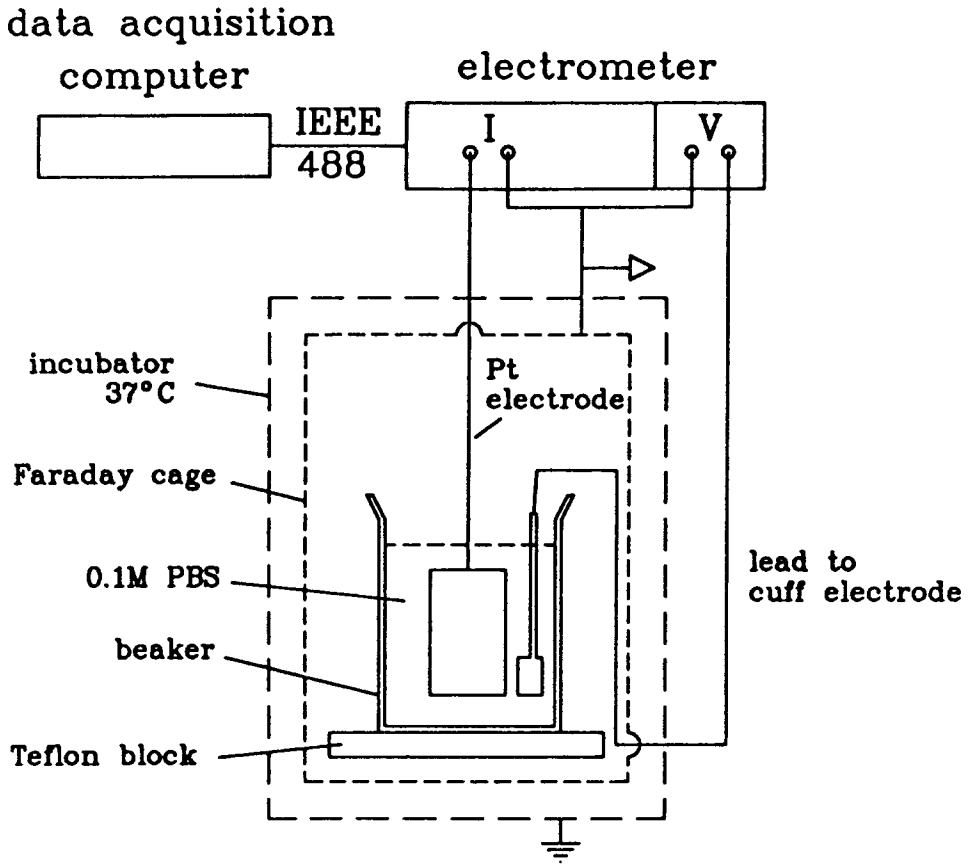

Figure 6. Schematic of the experimental system for leakage current measurements.

Initial results of the IV measurements indicated significant leakage through the Teflon® AF coating. Examination of the coatings by SEM revealed a moderately high density of pinholes. A significant reduction in the leakage current was obtained by using a three coat process. Current-voltage curves for cuffs with patterned TiIr metallization employing one and three coats of Teflon® AF are compared in Figure 7. The maximum leakage current under the worst case bias of -5 V is only 2×10^{-12} A. The absolute value of current is plotted in Figure 7 so that negative and positive currents can be represented on the same logarithmic plot. For comparison, the effect of the 3-layer Teflon® AF coating on leakage currents from a thermally oxidized Si wafer is shown in Figure 8. The Teflon® AF coating is effective in reducing the leakage current under both positive and negative bias to $<10^{-12}$ A. The magnitude of the leakage currents from the metallized cuffs are about the same as those on the Si wafer indicating effective coverage is obtained by spinning on flexible as well as rigid substrates.

Details of the time and temperatures schedule developed for densifying the Teflon® AF coatings are shown in Figure 9. The 260°C final anneal was not used on the undercoats since adhesion of subsequent layers is probably promoted by the slight plasticizing effect of residual solvent.

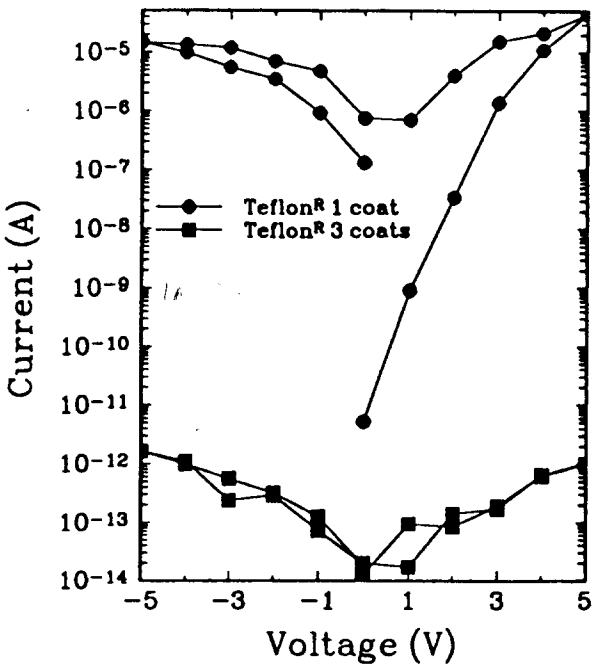

Figure 7. Steady-state leakage current through one and three layer Teflon® AF coatings over patterned TiIr metallization on FEP Teflon® cuffs.

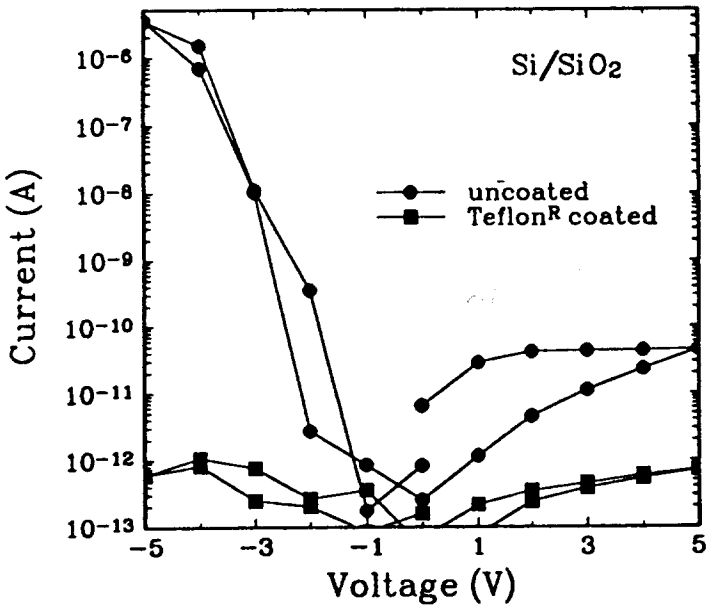

Figure 8. Steady-state leakage current through uncoated and a 3-coat layer of Teflon® AF on thermally oxidized Si wafer.

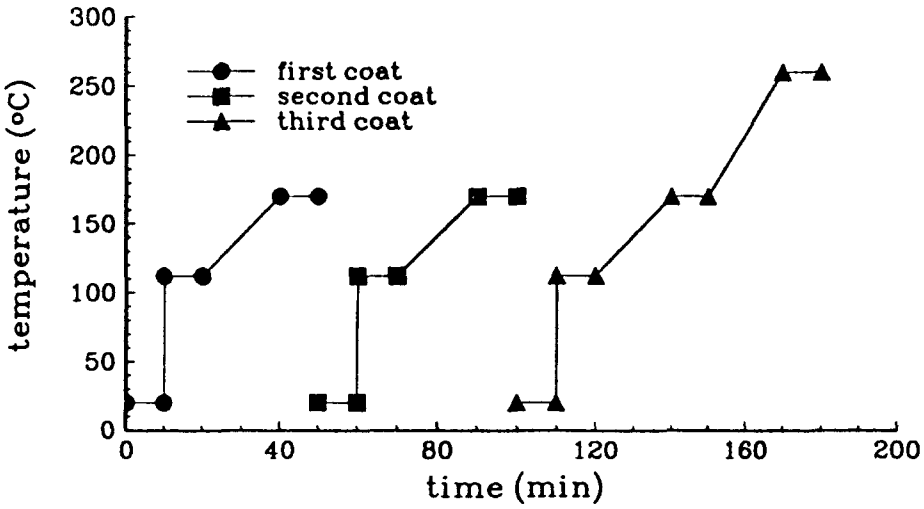

Figure 9. Time and temperature schedule for a 3-coat Teflon® AF process.

2.3.3 Thermoformimg Cuffs

Nerve cuffs could be fabricated from metallized FEP Teflon® substrates by thermoforming at 120°C. With spun Teflon® AF coatings on the inner surface, the thermoforming temperature had to be increased to 170°C. The appropriate planar shape for the cuff was cut from a metallized and patterned substrate and rolled into a tube to form the cuff. The cuff was inserted into an aluminum holder drilled with various holes of appropriate diameter to produce the desired cuff diameter and placed in a furnace at 120°C or 170°C for 30-45 minutes. The entire holder and cuff were then quenched in cold water. This thermoforming operation produced a permanent cuff that curled slightly over itself. The cuff could be opened with a pair of tweezers and released to reform around a cylindrical or near-cylindrical object. There was no evidence of delamination of the metallization or the Teflon® AF during thermoforming.

2.4 AIROF Charge Injection Sites

Many investigators are evaluating activated Ir oxide films (AIROFs) for charge injection because of their ability to pass considerable charge in a quasireversible manner without undergoing electrochemical degradation. *In vitro* electrochemical measurements using biphasic pulses suggest charge injection limits of ±2 mC/cm^2 for anodic-first and ±1 mC/cm^2 for cathodic pulses without electrolysis of water (Robblee and Rose, 1990; Beebe and Rose, 1988). The bipolar charge injection provided by the use of AIROF electrodes should allow the implementation of a broad range of stimulation protocols using small area electrodes. This should provide the greatest latitude in choice of stimulation protocols for selective recruitment and graded response.

The activation of Ti-Ir films on FEP Teflon® followed procedures that have been established previously at EIC Laboratories (Robblee, 1991). Sputtered Ti-Ir films were coated with photoresist which was photolithographically patterned to expose an 0.017 cm^2, circular electrode. The remaining photoresist was used to isolate the unexposed Ti-Ir film from the electrolyte. The

exposed electrode was immersed in an 0.3M Na_2HPO_4 solution at pH 9 and potentiostatically pulsed with a 1 Hz square wave between limits of -0.8 V and 0.75 V versus an SCE reference electrode. The activation time required to produce AIROF was quite short, typically 30 s or less.

Figures 10 and 11 compare the cyclic voltammetric behavior of a Ti-Ir electrode in 0.1M PBS before and after activation for 30 s. The post-activation voltammogram shows a significant increase in equilibrium charge capacity and the formation of a distinct redox couple associated with a valence change in the activated oxide. Acute charge injection using monophasic, capacitor coupled cathodic and anodic pulses were used to evaluate the AIROF coatings. The pulse duration was 100 μs and was applied at a rate of 50 pulses per second (pps). For the initial study, cathodal and anodal charge densities of 80 $\mu C/cm^2$ were used which corresponds to a geometric current density of 0.8 A/cm^2. Charge-balance was achieved by the discharge of an 0.2 μF capacitor in series with a 10 Ω current measuring resistor and the electrochemical cell. The capacitor discharge was accomplished by electronically shorting the output of the stimulator 20 μs after the cathodic pulse phase. A schematic diagram of the charge injection circuit is shown in Figure 12. The potential transients during charge injection were recorded with a digital oscilloscope in the AC coupled mode. A high input impedance electrometer was used to measure the open-circuit corrosion potential and the interpulse potential (IPP). In our test protocol, the IPP is measured as the average potential during pulsing as recorded by the analog electrometer. Since the pulse and capacitor discharge phases are only ~1% of the interpulse period, they do not significantly effect the IPP measurement. We find this method introduces less error than direct measurement with an oscilloscope in the DC mode, since the oscilloscope has a comparatively low input impedance. Following each potential transient measurement during the charge injection studies, the stimulation circuit was disconnected from the electrochemical cell and the open-circuit potential (V_{oc}) of the electrode was measured with the electrometer after allowing two minutes for the potential to stabilize. The V_{oc} measured this way provides an unambiguous measurement of the electrode potential from which the electrochemical condition of the electrode can be assessed.

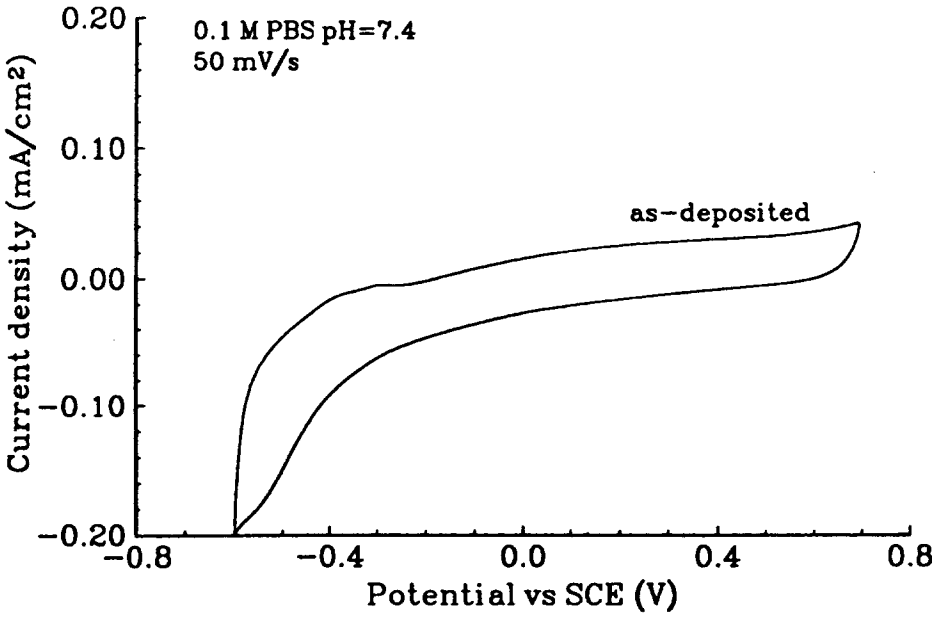

Figure 10. Cyclic voltammogram of as-deposited Ti-Ir on FEP Teflon® in 0.1M PBS. Sweep rate is 50 mV/s.

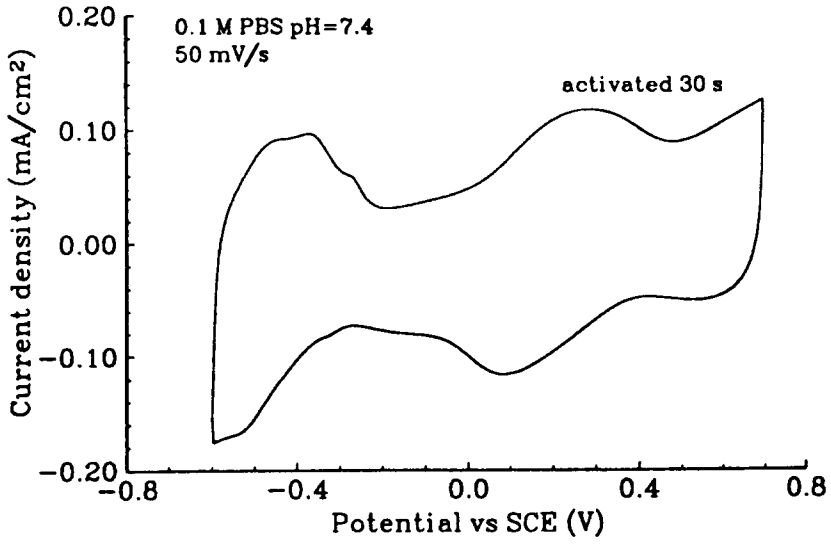

Figure 11. Cyclic voltammogram of Ti-Ir/AIROF on FEP Teflon® in 0.1M PBS following 30 s of activation.

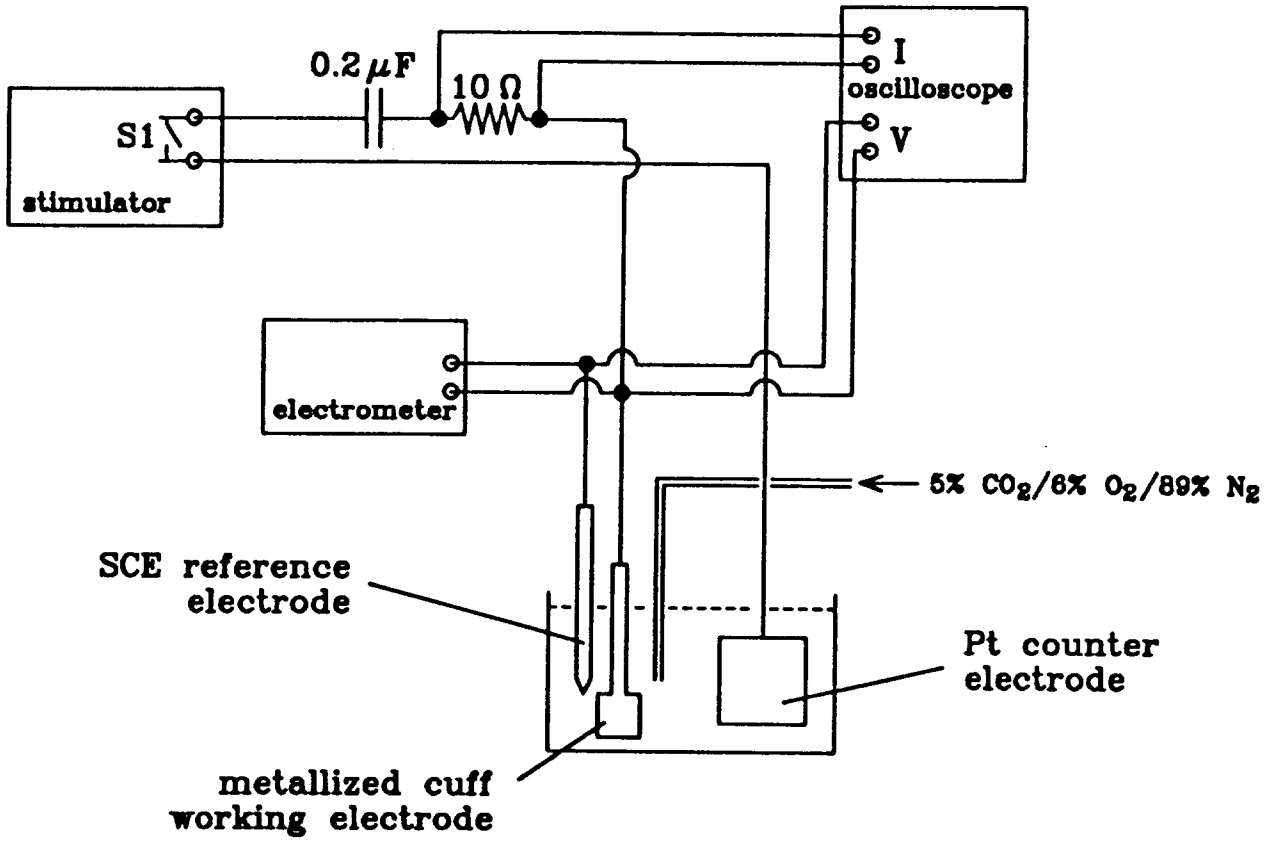

Figure 12. Schematic of the experimental arrangement used to record potential transient data.

The potential transient response of AIROF on Ti-Ir-coated Teflon® during sequential 6 hr and 5 hr cathodal and anodal charge injection periods, respectively, is presented in Table 5. After each hour of pulsing, the potential transient response was recorded. The pulsing was then interrupted and a cyclic voltammogram of the electrode recorded in the same electrolyte at a sweep rate of 50 mV/s between limits of -0.6 V and 0.7 V versus SCE. The CV data were integrated to determine the anodic and cathodic charge transfer on each half-cycle, $Q_a$cv and $Q_c$cv, respectively, in Table 5.

For both anodal and cathodal pulsing, the maximum potential excursions were within the water electrolysis limits of AIROF. The charge injection behavior of the electrodes varied very little throughout these acute studies. A small increase in the cyclic voltammetric charge capacity following anodal pulsing was observed which could be due to further activation of the underlying Ir or greater access to the existing AIROF from chemical or morphological changes associated with anodal charge injection. The access resistance was slightly lower for the anodal pulses because of the lower electronic resistivity of AIROF in its higher oxidation state. Based on an average anodic or cathodic charge capacity of ~2 mC/cm^2 during cyclic voltammetry, the 80 μC/cm^2 pulses are utilizing about 4% of the AIROF coating during charge injection. A comparison of cyclic voltammetric response of the AIROF electrode immediately after activation and following the charge injection studies detailed in Table 5 is shown in Figure 13. There is a small shift in the potential at which the primary redox peak occurs and some loss of peak definition on the cathodic sweep. The CVs are otherwise quite similar.

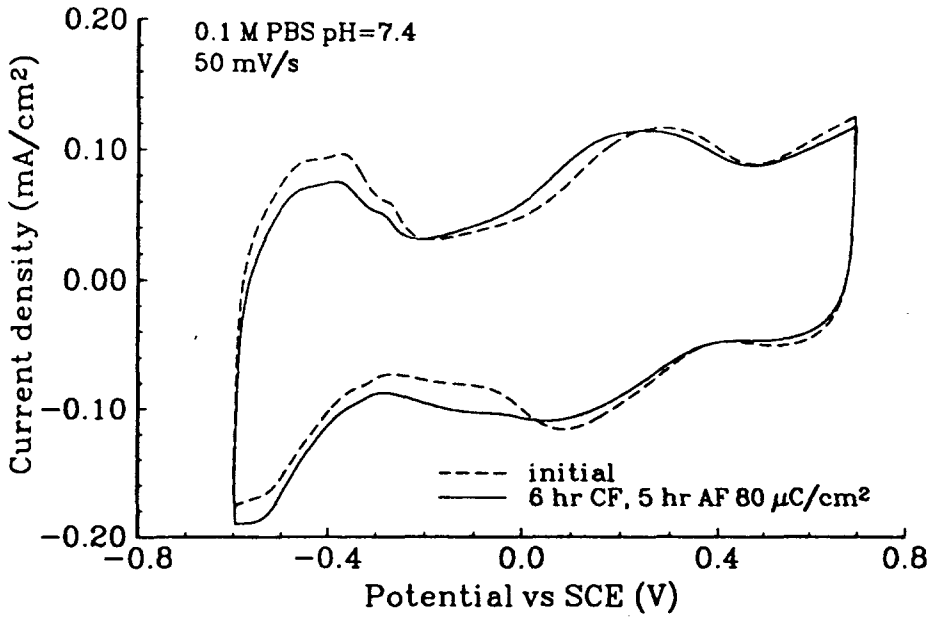

Figure 13. Comparison of cyclic voltammogram of Ti-Ir/AIROF on FEP Teflon® in 0.1 M PBS before and after 11 hr of charge injection.

Table 5. Potential transient response of AIROF on TiIr-coated FEP Teflon® for 80 $\mu C/cm^2$ capacitor-coupled, cathodal and anodal pulsing.

time hr	pulse direction	IPP V vs SCE	R_a Ω	$E_c$max V vs SCE	$E_a$max V vs SCE	V_{oc} V vs SCE	$Q_a$cv mC/cm^2	$Q_c$cv mC/cm^2
1	CF	0.076	209	-0.564		0.10	1.92	2.03
2	CF	0.098	209	-0.543		0.10	1.92	2.02
3	CF	0.086	203	-0.554		0.13	1.92	2.04
4	CF	0.092	203	-0.528		0.11	1.91	2.06
5	CF	0.092	209	-0.528		0.09	1.91	2.05
6	CF	0.085	209	-0.555		0.14	1.92	2.06
7	AF	-0.140	188		0.500	0.09	1.91	2.11
8	AF	-0.085	185		0.495	0.12	1.92	2.16
9	AF	-0.075	185		0.495	0.09	1.92	2.18
10	AF	-0.060	185		0.510	0.09	1.93	2.20
11	AF	-0.055	184		0.515	NA	1.94	2.21

CF - cathodic pulse
AF - anodic pulse
IPP - interpulse potential
R_a - access resistance
$E_c$max - maximum cathodic potential excursion
$E_a$max - maximum anodic potential excursion
V_{oc} - open-circuit potential (no pulsing)
$Q_a$cv - anodic charge capacity in a 50 mV/s cyclic voltammogram
$Q_c$cv - cathodic charge capacity in a 50 mV/s cyclic voltammogram
NA - data not available

By activating the TiIr electrodes for longer periods of time, higher charge injection capacities could be achieved without exceeding the potential window for H_2O electrolysis. Table 6 compares the cathodic-first charge injection capacities of AIROF on FEP Teflon® for activation times up to 2 minutes. A maximum charge injection capacity (Q_{inj}) of 250 $\mu C/cm^2$ was obtained for the 2 minute activation.

Table 6. Potential transient response of AIROF on TiIr-coated FEP Teflon® for different activation times. Pulsing is cathodic-first, capacitor-coupled, at 50 pps.

Activation Time s	IPP V vs SCE	Q_{inj} $\mu C/cm^2$
0	0.180	6
10	0.120	30
30	0.070	53
60	0.040	89
90	-0.080	161
120	-0.160	254

2.5 Histological Studies

In vivo studies of metallized cuffs implanted on the cat sciatic nerve were performed at the Hines Veterans Administration Hospital, Rehabilitation Research and Engineering Center as a subcontract on the present program. The objective of the study was to evaluate the tolerance of the nerve to mechanical and chemical damage associated with passive (no pulsing) nerve implantation. The principal investigator at Hines was Dr. James Walter. The report provided by Dr. Walter is provided below.

Thin-film peripheral nerve electrode - *in vivo* evaluation.

From: James S. Walter, Ph.D.

Collaborators: Jerry McLane, Ph.D.
Wuying Cai, M.D.
Michael Bednar, M.D.

Consultants: Charles Robinson, D.Sc.
Hans Thalhammer, DVM.
Talat Khan, Ph.D.

Introduction

With the expectation that functional neuromuscular stimulation (FNS) will restore movements of limbs, respiration, bowel and bladder function, the question of whether this technique causes nerve injury has been studied extensively. Several types of nerve electrodes have been evaluated including cuff electrodes (Hershberg, 1967; Hughes, 1980; Yuen, 1984), electrodes sutured along the nerve (Agnew 1993, 1989; Baer, 1990; Girsch, 1991; and Hershberg, 1967), and spiral electrodes (Bowman, 1985; Naples, 1988). The current authors have been using epimysial type electrodes to stimulate underlying nerves (Walter, 1991, 1989). A loss of nervous tissue to some extent has been observed in each of these studies. In a recent report, loss of a small percentage of neurons was associated with the connecting cable and mechanical injury indicated by a twisted cuff (Agnew, 1993; Koller, 1992).

The present study was undertaken in order to examine if a highly flexible thin film cuff might prevent injury to the nerve. A short cable of the same flexible material was also connected to the cuff. A short implantation period of six weeks was chosen as this should be sufficient to allow for the evaluation of degeneration of nerve fibers subsequent to implantation of the cuff and the development of a connective tissue sheath around the cuff and nerve (Baer, 1990).

An important second issue is adherence of sputter deposited metal coatings on Teflon® thin films. To evaluate adhesion, we implanted six small Teflon® plates that had been coated with various metal films under the cat skin.

Materials and Methods

Animals:

Three male cats (Hummel Creek Kennels, St. Louis, Missouri) weighing an average of 4.5 ± 0.26 Kg (mean ± S.E.M.) were anesthetized with 20 mg Ketamine hydrochloride/Kg and 2 mg xylazine/Kg body weight, intubated and put on a respirator for our implantation procedures. The animals were housed for 42 days (6 weeks) in standard cages and fed a standard cat diet with water.

Electrodes and Plates:

Cylindrical cuff electrodes with an electrode lead that was 4 cm in length were used. The inner diameter of the cylinder was 3.5 to 4 mm, the electrode length was 1.5 cm. The cuff was made of a thin (0.5 mm) film of Teflon® and was coated with titanium and iridium bilayer electrodes. The Teflon® was extended at one end to form the electrode cable in the form of a tab. The tab was 2 to 3 mm across and 3 to 4 cm long. Test plates were also implanted under the skin to evaluate adhesion of sputtered metal bilayers. The test plate coatings evaluated were the following: TiIr, TiAu, and TiPt.

Implantation:

The cuff was implanted on the right sciatic nerve in two of the animals and on the left nerve in the third animal. The sciatic nerve was exposed and isolated from surrounding fascia. Using an insertion tool, the cuff was positioned around the nerve as shown in Figure 14. Two of the animals required additional mechanical manipulation with forceps upon insertion. The cuff was inserted about 11 cm from the ischial tuberosity. There was no fixation to the epineurium of the nerve. The electrode lead (tab) was placed parallel to the nerve between the dorsal and the

adductor muscles of the thigh. In each of the three animals the opposite sciatic nerve was exposed and isolated from surrounding tissue without implanting electrodes (sham control operation).

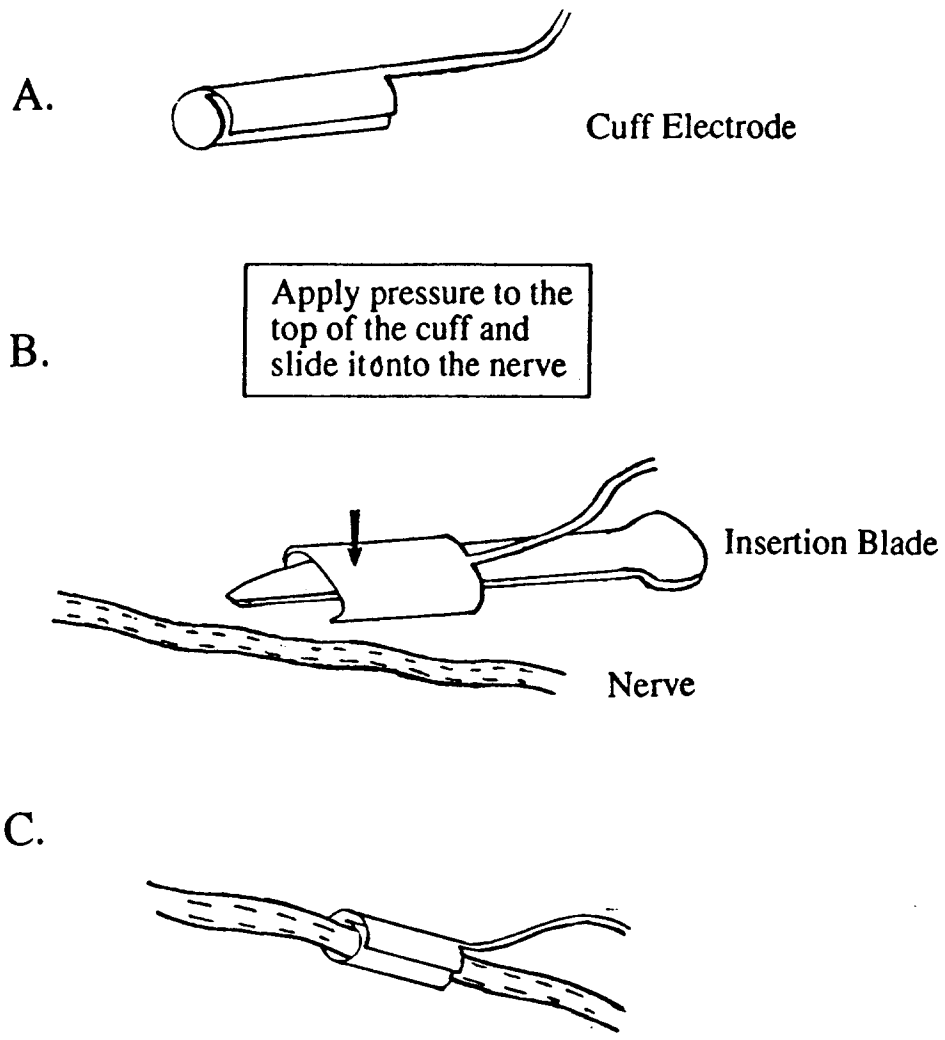

Figure 14. Nerve cuff insertion tool and implantation procedure.

Explantation:

No stimulation current was applied to any of the electrodes. Forty two days after implantation the animals were reanesthetized and perfused with 5% paraformaldehyde and 5% gluteraldehyde in 0.05M phosphate buffered solution using pressure generated by the perfusion medium elevated to 3.5 feet above the animal. Tissue was stored in 3% paraformaldehyde. The cuffs were removed from the nerves *in situ* in two of the animals. Two to three millimeter sections of the nerve were harvested 1 cm distal to the cuff, directly beneath the cuff and 1 cm proximal to the cuff. In the third animal, the cuff had come off the nerve and was found above the nerve

covered in a thick layer of connective tissue. However, sections of the underlying nerve were harvested as in the other two animals. For sham control, three specimens were harvested at the corresponding levels of cuff implanted animals, and all of the harvested tissues were prepared for histological examination.

Processing:

Nerves were post-fixed in 1% osmium tetroxide and embedded in plastic and stained with toluidine and basic fucin. For quantitative evaluation, 1 μm semi-thin cross-sections were cut on an ultramicrotome. Slides were evaluated on a Nikon microscope at magnification of 100 - 400X. For image analysis the image was transmitted by TV camera to a personal computer for planimetry measurements using the NIH Image 1.43 program. Cross-sections of the sciatic nerve at the level of the cuff were examined in regard to either signs of degeneration such as myelin fragmentation, reduction of nerve fiber density, and increase in connective tissue or signs of regeneration, e.g., groups of small fibers with thinned myelin sheaths (Baer, 1990).

The following parameters were measured for each specimen of the sciatic nerve: 1) total cross-sectional area of neural tissue within the perineural sheath; 2) area of nerve segments showing signs of de- or regeneration; 3) cross-sectional area of 200 - 300 nerve fibers (expressed as calculated diameter of a circle of the same area). The following data were calculated from these measurements: 1) percentage of altered area proportional to total area of neural tissue within the perineurium; 2) percentage of neural cross-sectional area occupied by myelinated axons (proportional to that captured by connective tissue) in control and experimental segments (nerve fiber density).

Results

Sciatic nerve:

In all three animals, connective tissue had grown around the cuffs and the sciatic nerve. However, none of the nerves showed any signs of edema proximal to the cuff. The thickest envelope of connective tissue was around the cuff that had come off the nerve (cat #3). The envelope was greater than 1 mm in some parts and was vascularized and pink. Much less connective tissue was observed around the cuffs that remained on the nerves. In cat #1, which had a snug fitting cuff, the nerve had a thin sheath both around the outside of the cuff and under the cuff. Considerably more connective tissue was located around the tab at the end of the cuff. In the second cat (cat #2), more connective tissue was present than in the first cat. The cuff on the nerve was 20 to 30% larger in diameter than the nerve and more connective tissue had grown under it between the nerve and the cuff. There was also a mass of connective tissue around the tab. All three of the contralateral, sham-control nerves were found in the thin fascial sheaths that the nerve normally lies in.

Alterations:

Six weeks after electrode implantation none of the cross sections of the sciatic nerve proximal to the electrode from the two cats exhibited any signs of injury (Table 7). Histological cross-sections are shown in Figure 15. However, note should be made of poor histological preparation across approximately 10-20% of this region. At the level of the electrodes, only one specimen showed an area of thickened myelin sheaths, suggesting degenerative processes. This segment captured 1% of the area in cat #1 and no comparable areas were found in cat #2. In cat #3, the histological preparation from the nerves was poor and morphometric measures could not be readily made. Axonal area density in representative areas on the nerve under the cuffs (19.22 ±3.93%) were not significantly different from axonal area densities (21.36 ±0.91%) at a

comparable level of the contralateral nerves. Measurement of axonal diameters within these segments indicated no shift toward smaller axons which would be indicative of regenerated fibers.

Cuffs:

Each of the three cuffs were easily taken out of the connective tissue that they were encapsulated in. The connective tissue did not adhere to the cuffs and there was no indication of any physical changes in the cuffs based on visual observation.

Plates:

Each of the Teflon® plates was covered by a thin encapsulation of connective tissue. The connective tissue did not adhere to the plates and the plates did not appear to be affected by the implantation following post-operative visual examination.

Discussion

The present study was done in order to quantify the short-term effects of a newly developed thin-film peripheral nerve cuff electrode on the integrity of peripheral nerves. The histological observation of the sham operated nerves suggested that implanting a thin-film cuff resulted in little difference in morphological effects compared to simple surgical exposure of a peripheral nerve. As no stimulation was applied to the electrodes the observed minor alterations can only be due to mechanical factors caused by the electrodes themselves.

The cuff came off one of the sciatic nerves, and in a second animal, increased connective tissue was noted around the nerve where a larger cuff was used. Both of these observations indicates that sizing is important and the cuffs should be approximately the same size as the nerve. This observation is supported by recent reports of minimal neural damage when snug, but modestly flexible, nerve cuffs are used (Agnew, 1989; Naples, 1990). Tissue fixation was a problem with some of the tissue and increased perfusion pressures will be used in the future.

Alterations:

Only one of the specimens of the sciatic nerve at the electrode level and distal to it, showed signs of morphological alteration. These alterations consisted of degenerating fibers, thus suggesting mechanical injury at the time of the implantation or during chronic implantation. In no case was more than 1% of the cross-sectional area of the nerve found to be altered. Reduced nerve fiber density at the electrode level was not observed. Comparing the results of the present study with those obtained with other electrodes both cuff and epineural (Girsch, 1991; Hughes, 1980; Koller, 1992; Yuen, 1984), no increase in altered nerve segments was observed.

Clinical Implications:

Concerning the nerve dimensions, the sciatic nerve of the cat is similar to the human median nerve. Probably nerve functional regeneration proceeds faster in small cats, but the general tendency of nerve fibers to regenerate after injury is the same even in humans. In addition, there is no evidence that the peripheral nerves of cats are more or less vulnerable than human nerves to injury. So the main results of the present study, based on the limited alterations of nervous tissue to the implanted cuff electrode during the 6 weeks of implantation, indicated that properly sized cuffs will not cause mechanical damage to peripheral nerves. However, the effects of longer test periods as well as the effects of electrical stimulation require evaluation.

Table 7. Summary of lesions observed in three cats sciatic nerves six weeks after electrode cuff implantation. Altered and normal areas expressed in percent of the total cross-sectional area within the perineural sheath.

CONDITION	% NORMAL[a]		% INJURY[b]		% ARTIFACT[c]	
	cat 1	cat 2	cat 1	cat 2	cat 1	cat 2
CUFF						
LEVEL 1 (proximal)	80.7	90	0	0	19.3	10
LEVEL 2 (under cuff)	92.9	100	0.7	0	6.4	0
LEVEL 3 (distal)	100	NA	0	NA	0	NA
SHAM CONTROL						
LEVEL 1	100	100	0	0	0	0
LEVEL 2	99.4	100	0	0	0.6	0
LEVEL 3	97.8	100	0	0	2.2	0

[a] percentages of normal injured and artifact was determine based on area measures.

[b] Injury was indicated by thick myelin sheet around nerve with preliminary degeneration.

[c] Artifact was indicated by poor fixation or embedding.

NA - tissue not available

Cat 1, good fitting nerve cuff on nerve, thin connective tissue sheath on cuff.

Cat 2, large nerve cuff on nerve, thick connective tissue sheath on cuff.

Cat 3, cuff was found off of the nerve heavily covered with connective tissue.

Note, in cat #3, visual observation of the nerve indicated no swelling or adverse connective tissue, however, the histological preparation from the nerves was poor and morphometric measures could not be readily made.

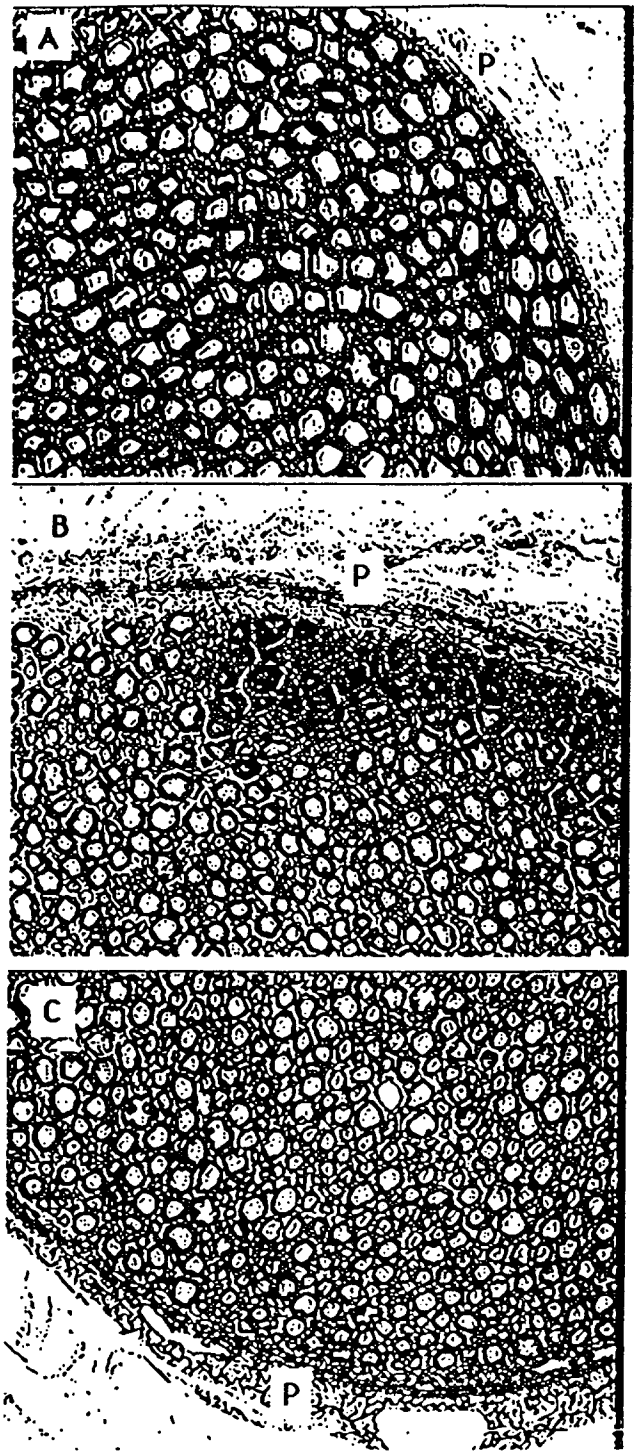

Figure 15. Light micrograph of normal and degenerating tissue. Nerves from three areas are shown. A. Sham control nerve from contralateral side. B. Nerve from under the cuff (cat #1) showing a small area of neural degeneration indicated by thick myelin. These cells can be seen adjacent to the perineurium (P). C. Same as B but area with no apparent injury.

3.0 TECHNICAL FEASIBILITY

The objective of the Phase I program was to establish the technical feasibility of the proposed cuff electrodes by demonstrating their manufacture on flexible, thermoformable polymer substrates using thin film processing methods. A further objective was an acute (6 week) *in vivo* evaluation of the tolerance of the cat sciatic nerve to implantation of the cuff.

During the Phase I program, approximately 12 cuffs were manufactured. Three of these were used for animal studies at the Hines V.A. Rehabilitation Engineering Center and the remainder used at EIC Laboratories for evaluating adhesion of metallization and the barrier properties of dielectric coatings (i.e., PECVD oxides, Teflon® AF). The technical accomplishments of the Phase I program relating to the feasibility of the proposed cuff electrodes are the following:

- demonstration of sputtered TiIr metallization on FEP Teflon® that can be photolithographically patterned and is adherent following extended soaking in PBS at 90°C and steam sterilization;
- demonstration of sputtered TiIrTiAu four-layer metallization as a high electrical conductivity lead component for the cuff that is adherent following 90°C soaking in PBS and steam sterilization;
- activation of TiIr metallization on FEP Teflon® to be produce AIROF charge injection coatings;
- demonstration of spun Teflon® AF coatings as an inner surface dielectric to electrically (electronic and ionic) isolate metallization on the cuff;
- fabrication of cuffs from metallized and Teflon® AF coated polymer films by thermoforming;
- demonstration of passive tolerance of peripheral nerve to cuff implantation in acute (6 week) animal studies.

Although the Phase I program was reasonably successful in demonstrating the feasibility of the cuffs, several materials and manufacturing issues require further study. These include:

- the effect of sputter deposition conditions on the morphology and residual stresses of metallization;
- the development and chronic testing of AIROF charge injection coatings at higher charge densities than was demonstrated in the Phase I program;
- the development of an adherent metallization using Pt as the charge injection electrode.

Chronic *in vivo* evaluation of the cuffs for both materials stability and physiological tolerance is required and would be a major objective of a Phase II effort. In regard to acute and chronic animal studies for evaluation of selectivity in grasp, a major technical consideration is electrical connection to the cuff. *In vivo* electrical connections are a significant concern with implanted FES systems and considerable effort has been expended in the development of reliable interconnect systems. In the Phase I program, reliable acute electrical connection between the individual conductors of a Teflon® coated multistrand stainless steel lead and the metallized cuff

was made by wrapping the stainless steel lead in a tight coil around the metallized shank on the cuff and encapsulating with silastic. This approach, although unlikely to be satisfactory for chronic applications, would be used to expedite acute *in vivo* testing in a Phase II program.

Commercial opportunities for nerve cuff electrodes seem quite significant. Applications involving neuromuscular stimulation in spinal cord injury include restoration of grasp and gait. Other areas where significant potential exists include: dynamic cardiomyoplasty where electrical stimulation of the latissimus dorsi is used to effect myocardial contraction (De Luca, 1992; Letsou, 1992); sacral root stimulation for bladder control; vagus nerve stimulation for the treatment of epilepsy (Tarver, 1992) and, pacing of the phrenic nerve (Baer, 1990). The proposed thin film fabrication process allows a wide variety of electrode geometries to be implemented for different FES applications without redesign of the basic cuff. The extent to which nerve cuff electrodes will be used clinically will depend greatly on their efficacy with respect to selective, graded, and physiologically ordered stimulation. Recent reports suggest that cuff electrodes on peripheral nerve trunks can achieve both selective and physiologically ordered recruitment in some applications (Sweeney 1990; De Luca, 1992).

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